



*Producers of Quality  
Nonprescription Medicines and  
Dietary Supplements for Self-Care*

## CONSUMER HEALTHCARE PRODUCTS ASSOCIATION

*Formerly Nonprescription Drug Manufacturers Association*

April 26, 1999

Dockets Management Branch  
HFA-305  
Food and Drug Administration  
5630 Fishers Lane Room 1061  
Rockville, MD 20852

Re: Docket No. 99N-0386, Talking with Stakeholders  
about FDA Modernization: Notice of Meetings and  
Teleconference. Federal Register 64: 13804-13806, 1999.

Dear Madam or Sir:

These comments are submitted by the Consumer Healthcare Products Association (CHPA) to the Food and Drug Administration (FDA) in response to FDA's announcement of a live satellite teleconference and meetings in eight major cities across the country as a means for the agency to answer questions from viewers and listen to suggestions about how FDA can better carry out its mandates.

CHPA, formerly known as the Nonprescription Drug Manufacturers Association (NDMA), is the 118-year-old trade organization representing the manufacturers and distributors of national and store brand dietary supplements and nonprescription medicines. CHPA's membership includes over 200 companies involved in the manufacture and distribution of these self-care products and their affiliated services (e.g., raw material suppliers, research testing companies, contract manufacturing companies, advertising agencies, etc.).

FDA asks five questions for specific comment by stakeholders taking part in the teleconference and meetings. CHPA supports the dialogue in each of these areas, but

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focuses in these written comments on three questions relating to science-based decisions. Specifically FDA asks:

1. "What actions do you propose the Agency take to expand FDA's capability to incorporate state-of-the-art science into its risk-based decision-making?"
2. "What actions do you propose to enable FDA and its product centers to focus resources on areas of greatest risk to the public health?"
3. "What additional actions do you propose for enhancing communication processes that allow for ongoing feedback and/or evaluation of our modernization efforts?"

Our comments request specific actions under sections I.A. and III, below, relating to needed refinements on CDER's<sup>1</sup> handling of Rx-to-OTC switch decisions and CFSAN's<sup>2</sup> development of a MaPP on meetings with external constituencies. We also urge continued support by the agency on joint educational efforts in the compliance area, and support CFSAN's program priority for developing an overall strategy on dietary supplements. Section IV provides a list of our requested actions.

**I. FDA Question: What actions do you propose the Agency take to expand FDA's capability to incorporate state-of-the-art science into its risk-based decision-making?"**

CHPA has two separate comments in answer to the question of expanding FDA's capability to incorporate state-of-the-art science into its risk-based decision-making. The first relates to Rx-to-OTC switch and FDA's recent action that questions the basic approach FDA is taking to benefit/risk-based decision-making relating to OTC

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<sup>1</sup> CDER: Center for Drug Evaluation and Research.

<sup>2</sup> CFSAN: Center for Food Safety and Applied Nutrition.

availability. The second relates to CHPA's continued support for industry-agency partnerships relating to joint educational efforts on technical aspects of good manufacturing practices in order to ensure a mutual understanding of, and commitment to, the best applied technology in Good Manufacturing Practices.

#### **A. Rx-to-OTC Switch**

In its March 1999 "A Message to FDA Stakeholders: FDA's Progress in Implementing FDAMA," FDA states:

"Science-based decisions are made throughout the life span of products from initial research, development and testing, through production, marketing and consumption. These decisions require the best science to identify, evaluate and balance product risks and benefits. It is crucial that FDA's staff in collaboration with product sponsors develop a shared understanding of new science and technologies and their effect throughout a product's life span. What actions do you propose the Agency take to expand FDA's capability to incorporate state-of-the-art science into its risk-based decision-making?"

In the same document, FDA states that "Dr. Henney places a high premium and priority on making sure that science anchors FDA's decision-making processes and critical policy decisions. CHPA strongly supports this public health objective, particularly as it applies to the reclassification of prescription products to nonprescription status (i.e., Rx-to-OTC switch).

CHPA proposes<sup>3</sup> that FDA establish a CDER policy that would require the agency to fully explain its positive and negative switch decisions and in the process to reconsider its Guidance for Industry on the "OTC Treatment of Hypercholesterolemia"

and thereby further ensure that a data-driven process is used throughout the agency to permit selected prescription drugs, including cholesterol-lowering drugs, to be available OTC in the future. Such a policy would articulate the long-standing approach that FDA has used for most, if not all, Rx-to-OTC switch decisions -- a case-by-case, weight-of-the-evidence, data-driven, dialogue-driven approach.

The public health history of Rx-to-OTC switch has been exemplary. Since 1972 at the beginning of the OTC Review and through the subsequent further development of the OTC NDA process of drug approval, over 78 ingredients, dosage forms, dosages and indications have been switched from Rx-to-OTC status (see Attachment). With the exception of metaproterenol, which was switched and then switched back to Rx status in 1983 largely on the basis of medical opinion vs. data<sup>4</sup>, Rx-to-OTC switch ingredients have had a remarkable success story, providing significant cost savings to the public health system<sup>5</sup> and important self-care therapeutics for the consumer (e.g., fluoride, vaginal antifungals, nicotine-replacement therapy, cromolyn sodium for prevention of allergy symptoms, among many others).

Importantly, under the Durham Humphrey Amendments to the FD&C Act, any drug which cannot be safely used without medical supervision must be labeled for sale and be dispensed only by prescription of a licensed practitioner; otherwise it is OTC. Hence, by law and regulation in the United States, drugs are prescription by exception.

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<sup>3</sup> See also comments from CHPA (formerly NDMA) to FDA Docket No. 98N-0044: Regulations on Statements Made for Dietary Supplements Concerning the Effect of the Product on the Structure or Function of the Body. *Federal Register* 63: 23624-32, April 29, 1998.

<sup>4</sup> "Despite the advisory committee's vote, FDA continues to believe that a careful weighing of risks and benefits supports the proposal that metaproterenol sulfate metered-dose inhaler should be made available to asthma sufferers without a prescription. Metaproterenol sulfate is a safe and effective drug, and nothing in the criticisms submitted to FDA or voiced at the advisory committee meeting is inconsistent with that judgment. ... Nevertheless, FDA cannot fail to respect the judgment of specialists in the field who believe that OTC availability of metaproterenol sulfate metered-dose inhaler poses a health risk. These practitioners have made clear that they have important reservations about FDA's decision to propose that metaproterenol sulfate be marketed OTC." Proposed Rule and Related Notice re Over-the-Counter Marketing Status of Metaproterenol Sulfate Metered-Dose Inhaler Drugs For Use as a Bronchodilator [48 F.R. 24925-28 (6/3/83)].

<sup>5</sup> Kline & Company, Inc.; Economic benefits of self medication. A final report to NDMA, May 15, 1997 - on file at CHPA.

In other words, "If it can be OTC, it must be OTC." The law, however, does not state the approach that FDA should take in determining why a drug cannot be safely used without medical supervision. However, the applied approach by CDER has been for most, if not all, Rx-to-OTC switch decisions a case-by-case, weight-of-the-evidence, data-driven and dialogue-driven process to determine OTC availability. This approach is entirely consistent with the legal mandate that, if a product can be OTC, it must be OTC.

Because FDA has demanded an ever-increasing data base to support more complicated switch decisions, the proposition that a product or condition can be switched to OTC or self-care status can be regarded a testable hypothesis. Mutual recognition of this concept by CDER and industry is vital if Rx-to-OTC switch is to be a viable approach for future OTC product introductions.

In other words, OTC availability is usually distilled to a basic question (or questions) that, if tested, would contribute meaningfully to OTC benefit/risk decisions pertaining to OTC availability. For example, drugs may show relatively modest improvements in symptoms over placebo in controlled trials, and the potential OTC safety concerns for an Rx parent of the switch candidate are relatively well characterized through its Rx marketing experience (e.g., potential drug-drug interactions, development of viral resistance, masking of more serious conditions, etc.). Thus, the testable switch hypothesis might be: Does the OTC availability of candidate "X" result in an unreasonable level of excess cases going undiagnosed? We have the available tool to test (i.e., disprove) this hypothesis – the actual use study, wherein OTC usage in a simulated OTC environment can be compared to that in a simulated Rx environment. Other questions, perhaps relating to effectiveness, might also have to be tested and added to a distilled benefit/risk question, such as: Is a modest (x%) improvement in one or more specific clinical endpoints related to self-care of the condition or disease under study worth the unlikely (but perhaps uncertain) risk of a particular side effect (e.g., GI side effects, drug-drug interaction, etc.) or consequence (e.g., unacceptable level of undiagnosed cases, or viral resistance, etc.)?

With this approach, the need for a health professional as a learned intermediary in the use of any drug for a potential or actual OTC condition is a testable hypothesis. Scientific and clinical data - not medical opinion alone - are the drivers for expanding the OTC paradigm with novel Rx-to-OTC switches.

However, on October 21, 1997, FDA issued a Guidance for Industry on the "OTC Treatment of Hypercholesterolemia" that stated:

"It is CDER's view that (a) health care practitioner supervision in the diagnosis and ongoing management of hypercholesterolemia is essential for safe and effective use of drug products to treat this condition and (b) this supervision is assured within the context of prescription access to the appropriate drug(s) for the individual patient. CDER therefore believes that drugs for the treatment of hypercholesterolemia should not be sold OTC in the United States."

This decision was made after review by an FDA advisory committee of a comprehensive, well-designed, well-conducted actual use study that showed a remarkable set of study results supporting the safety and effectiveness of Questran for OTC use, as well as an equally remarkable level of interest by the American public in having widely available cholesterol-lowering agents.

This decision and subsequent "guidance" on OTC hypercholesterolemic agents comes at a time when the agency is grappling with claims for dietary supplements, specifically statements of nutritional support (or structure/function claims). While the Association has stated its firm support for the provisions of the Dietary Supplement and Health Education Act (DSHEA) in comments to the agency on these types of dietary supplement claims (see footnote 3) and has urged an alternate proposal to their

regulation, CPHA's comments and FDA's proposal share the basic concept of permitting dietary supplements to make claims relating to cholesterol levels.

Further, prescription drugs can make cholesterol claims, as can foods as well as dietary supplements. OTC drugs cannot. CHPA urges FDA to consider the incongruity of this situation. An OTC drug for lowering cholesterol levels would be labeled with ample information approved by FDA, fit the OTC paradigm that in selected cases requires a physician visit prior to use (e.g., as in the case of OTC antifungals for vaginal candidiasis), and be tested through appropriately designed label comprehension and actual use studies. A dietary supplement may make maintenance claims for cholesterol levels without FDA review. While CHPA supports such a claims structure for dietary supplements under DSHEA, the Association believes that to regulate sensibly, the agency must consider the bigger picture, taking account of the full range of products available for health care. Foods, dietary supplements, OTC drugs, and prescription drugs are all part of the self-care product continuum. All of them, except OTC drugs, currently may make, or would be able to make under FDA's structure/function proposal, cholesterol-related claims.

FDA's declaration in its Guidance document that OTC drugs do not fit in this continuum does not make sense from a public health policy standpoint, especially against the background of the Questran studies described above that supported a switch NDA. CHPA believes cholesterol-lowering drugs are appropriate for OTC use and would contribute significantly to consumer health and understanding of disease. CHPA urges FDA to rescind its Guidance for Industry on the "OTC Treatment of Hypercholesterolemia" and instead explain in detail the specific questions that would have to be answered by well-designed research before drugs for hypercholesterolemia can be made available without a prescription. Only in this way can the dialogue- and data-driven process that has characterized Rx-to-OTC switch over the last 25 years be preserved.

In enacting DSHEA, Congress recognized the need to maintain a balance between providing expanded self-care opportunities to consumers through dietary supplements on the one hand and preserving incentives for drug research and development on the other. FDA's decision on the switch of Questran and its Guidance for Industry on the "OTC Treatment of Hypercholesterolemia" declaring that such drugs should not be sold OTC in the United States is a frank disincentive to research and development in other potential switch areas, where dietary supplement products make structure/function claims in the same general category. Congress did not intend for FDA to chill drug research and development that could benefit consumers.

Therefore, in answer to FDA's question, "What actions do you propose the Agency take to expand FDA's capability to incorporate state-of-the-art science into its risk-based decision-making?", CHPA asks that FDA recapture its long-standing data-driven, dialogue-driven approach to Rx-to-OTC switch decisions by ensuring a CDER policy that would require the agency to fully explain its negative switch decisions, in order to identify limitations and omissions in the sponsoring company's submission. In this way, when confronted with a negative switch decision, a company has the opportunity to determine what further, if any, state-of-the-art research might be undertaken to support a re-proposal for OTC availability of a prescription drug active ingredient – consistent with the FDC Act that, if it can be OTC, it must be OTC and consistent with the premise that switch is essentially a testable hypothesis. FDA would thus be assured of having the best science to support its benefit-risk decisions about OTC availability of drug products. In the process of developing such a CDER policy, the negative guidance on OTC antihypercholesterolemics would be appropriately rescinded and presumably amended.

We look forward to the agency's response on this point.

## **B. Applied Technology and Good Manufacturing Practices**

CHPA has had a long-standing partnership with the CDER Office of Compliance in terms of joint educational efforts, including CHPA's annual Manufacturing Controls Seminar (now in its 31<sup>st</sup> year), industry briefings, Small Business seminars, and regional meetings on specific issues identified as current manufacturing problem areas. These sessions have been invaluable. They have also shown an important approach to building the science base of the agency, through the collaboration of FDA with leading industry scientific/technical experts.

Our goal is to address current problem areas or evolving technological issues and create joint educational meetings with the agency in order to raise awareness about the identified issues, establish a higher level of understanding of the agency's expectations for current Good Manufacturing Practices, and share scientific advances in the production of quality drug products. Such jointly developed educational meetings allow the agency to make use of state-of-the-art scientific expertise already available in the industry.

These efforts have an important salutary effect on product quality. A notable example of the practical benefits of this joint educational approach was seen following the 1988 joint regional seminars on label mix-ups. The frequency of what had been the number one cause of product recalls dropped dramatically. We also understand that our programs and those of other associations are regarded by the Office of Compliance as important preventive compliance vehicles.

In sum, we ask FDA to continue its commitment to these types of partnerships with industry. Not only do such educational activities have a direct positive impact on product quality, thereby serving FDA's mission to protect the public health, they do so in a value-added way by saving agency resources, since industry assumes the administrative and financial burdens while providing input to FDA on the latest industry technology.

**II. FDA Question: "What actions do you propose to enable FDA and its product centers to focus resources on areas of greatest risk to the public health?"**

While CHPA does not believe that dietary supplements in general represent an area of greatest risk to the public health, the Association takes this opportunity to comment on a related area identified by CFSAN in its 1999 Program Priority document. Occasionally, certain ingredients, such as GBL, may be marketed as dietary supplements and FDA must take appropriate action to protect the public health. To do this consistently and coherently, FDA must have an overall strategy on dietary supplements, as suggested in CFSAN's Program Priority document. Our comments address this point.

In January, 1999, the Center for Food Safety and Applied Nutrition (CFSAN) published its 1999 Program Priorities document in which it stated as a Priority A activity its intention to "develop an overall strategy for achieving effective regulation of dietary supplements under the Dietary Supplement and Health Education Act (DSHEA)" by addressing "all elements of the dietary supplement program, including: boundaries between a dietary supplement and a conventional food, between a dietary supplement and a drug, and between a dietary supplement and a cosmetic product; claims; good manufacturing practices; adverse event reporting, review and follow-up; laboratory capability; research needs; enforcement; and resource needs." CFSAN also identified "stakeholder outreach" for both obtaining input to an overall strategy and effective communication. CHPA strongly supports a stakeholder outreach process to address these Priority A activities for CFSAN.

At the March 25, 1999, hearing of the Government Oversight Committee, both Dr. Henney and CFSAN's director, Mr. Joe Levitt, stated the agency's intent to develop this overall strategy in 1999. Given the effective operations of CFSAN in implementing the President's Food Safety Initiative, we are encouraged that the Priority A activity on dietary supplements might be undertaken by a similar administrative approach designed to define the agency's policy, operations and implementation plan through stakeholder

input. In this way, stakeholders can help define the needed priorities on dietary supplements, thereby allowing the agency to efficiently focus its resources. As FDA moves forward in this area, CHPA will provide specific detailed comments on FDA's overall strategy for dietary supplements.

**III. FDA Question: "What additional actions do you propose for enhancing communication processes that allow for ongoing feedback and/or evaluation of our modernization efforts?"**

Recent meetings between the Center for Food Safety and Applied Nutrition and CHPA have been excellent in content and form. Our response to this question is therefore not a criticism but rather a suggestion based on an association's view of the workings of two of the agency's main Centers – CFSAN and CDER.

Several years ago, CHPA worked with CDER in developing a MaPP for meetings by CDER with its external constituencies (MaPP 4512.1). This MaPP, which was subsequently updated with provisions from FDAMA, has been very successful in ensuring efficient meetings with defined agendas and questions, as well as subsequent action items. We encourage CFSAN to adopt a similar MaPP, as a proactive management step.

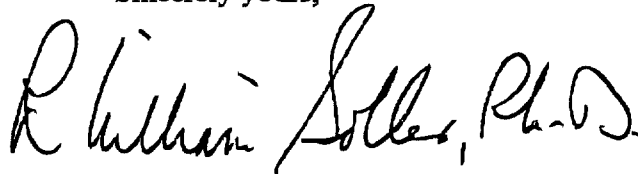
**IV. Conclusion and Requested Actions**

In conclusion, CHPA thanks FDA for the opportunity to provide the view of the consumer healthcare products industry. We look forward to feedback from the agency on our four areas of comment. We request that FDA:

- Develop of a CDER policy that would require the agency to fully explain its negative switch decisions in order to identify limitations and omissions in company submissions;

- In the course of developing such a guidance, rescind and presumably amend the negative guidance on OTC antihypercholesterolemic agents;
- Continue the agency's commitment to educational partnerships with industry;
- Engage, as planned, in a stakeholder outreach approach to developing an overall strategy on dietary supplements;
- Develop a "meetings MaPP" for CFSAN, similar to MaPP 4512.1 used by CDER.

Sincerely yours,

A handwritten signature in black ink that reads "R. William Soller, Ph.D." The signature is written in a cursive, flowing style.

R. William Soller, Ph.D.  
Senior Vice President  
Director of Science and Technology

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